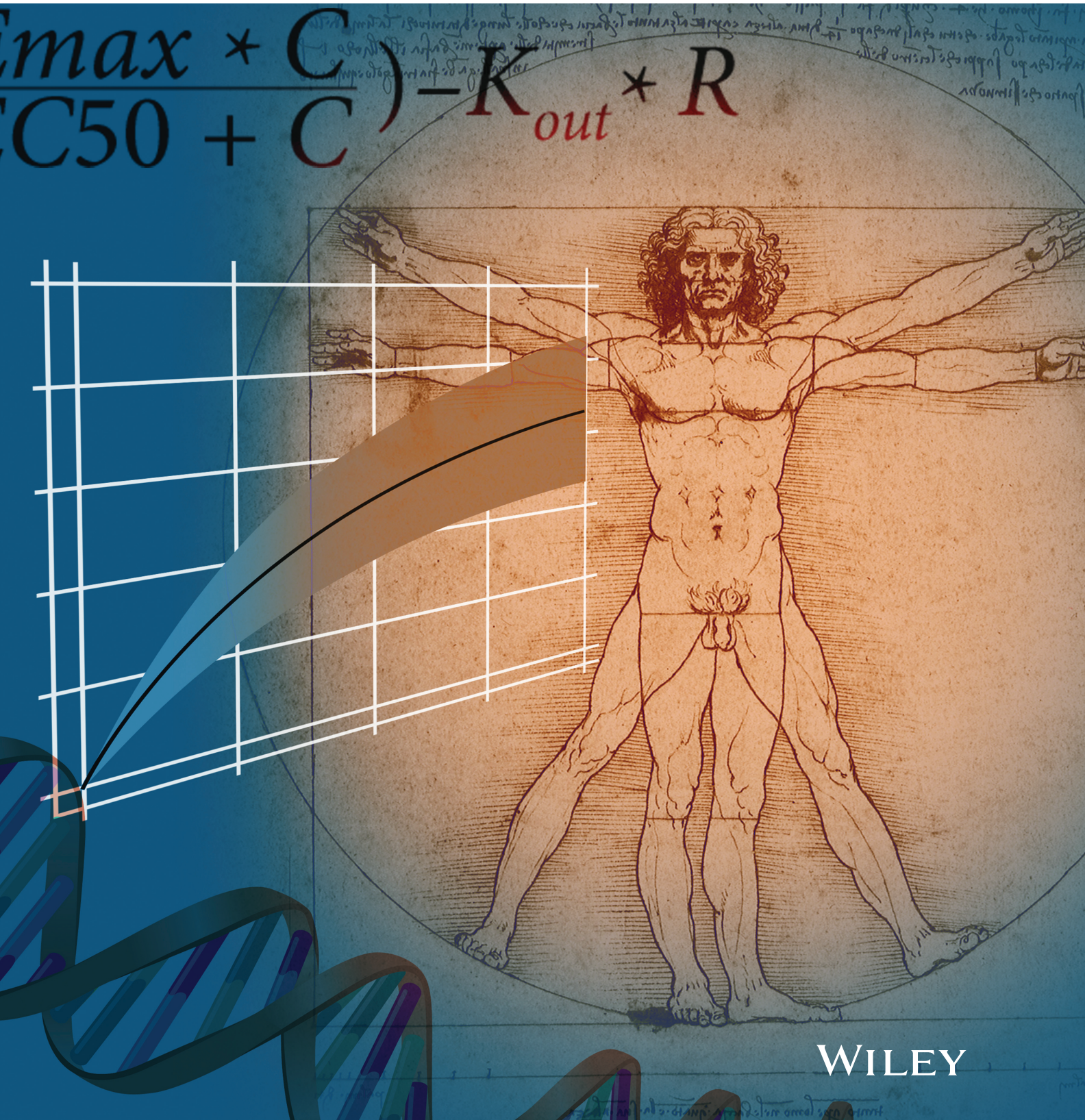
An Official Journal of ASCPT and ISoP

CPT: Pharmacometrics & Systems Pharmacology

Open Access



CPT: Pharmacometrics & Systems Pharmacology

WILEY

Editor-in-Chief

Piet van der Graaf, PhD, PharmD, *Leiden University, The Netherlands and Certara, United Kingdom*

Deputy Editor-in-Chief

Lena Friberg, PhD, *Uppsala University, Sweden*

Associate Editors

Stephen Duffull, PhD, *University of Otago, New Zealand*
Douglas A. Lauffenburger, PhD, *Massachusetts Institute of Technology, USA*
Lang Li, PhD, *Indiana University School of Medicine, USA*
Donald Mager, PharmD, PhD, *University at Buffalo, State University of New York, USA*
France Mentré, MD, PhD, *University Paris Diderot, France*
Vikram Sinha, PhD, *Merck & Co., USA*
Paolo Vicini, PhD, *MedImmune, United Kingdom*
Ping Zhao, PhD, *Food and Drug Administration, USA*

American Society for Clinical Pharmacology and Therapeutics

Chief Executive Officer
Sharon J. Swan, *Alexandria, VA*

Chief Operating Officer
Elise S. Laffman-Johnson, *Alexandria, VA*

Managing Editor
Emma P. Shumeyko, *Alexandria, VA*

Senior Editorial Coordinator
Rachel Taylor, *Alexandria, VA*

Editorial Board

Sandra Allerheiligen, PhD, *Merck Research Laboratories West Point, PA, USA*
Ioannis Androulakis, PhD, *Rutgers University Surgery, UMDNJ-RWJ Medical School Piscataway Township, NJ, USA*
Joseph P Balthasar, PhD, *University of Buffalo Buffalo, NY, USA*
Jeffrey S. Barrett, PhD, FCP, *The Children's Hospital of Philadelphia, Philadelphia, PA, USA*
Robert Bies, PharmD, PhD, *Indiana University Bloomington, IN, USA*
Kim L. R. Brouwer, PharmD, PhD, *University of North Carolina at Chapel Hill Chapel Hill, NC, USA*
Jenny Chien, PhD, *Eli Lilly & Co. Clinton, IN, USA*
David Z. D'Argenio, PhD, *University of Southern California Los Angeles, CA, USA*
Oleg Demin, PhD, *CSO Institute for Systems Biology SPb Moscow, Russia*
Paolo Denti, PhD, *University of Cape Town Cape Town, South Africa*
Hartmut Derendorf, PhD, *University of Florida Gainesville, FL, USA*
James M. Gallo, PharmD, PhD, *Albany College of Pharmacy and Health Sciences, Albany, NY, USA*
Christine Garnett, PhD, *Certara St Louis, MO, USA*
David Gavaghan, PhD, *University of Oxford Oxford, United Kingdom*
Ekaterina Gibiansky, PhD, *QuantPharm LLC North Potomac, MD, USA*
Pascal Girard, PhD, *Merck Institute for Pharmacometrics - Merck Serono S.A.Lausanne, Switzerland*
Manish Gupta, PhD, FCP, *Bristol-Myers Squibb; Lawrenceville, NJ, USA*
Bart Hendriks, PhD, *Merrimack Pharmaceuticals Cambridge, MA, USA*
Nicholas H.G. Holford, MBChB, *The University of Auckland Auckland, New Zealand*
Brett Howell, PhD, *The Hamner-UNC Institute for Drug Safety Sciences Research Triangle Park, NC, USA*
Matt Hutmacher, PhD, *Ann Arbor Pharmacometrics Group Ann Arbor, MI, USA*Jin Yan Jin, PhD, *Genentech, Inc San Francisco, CA, USA*
Kristin Karlsson, PhD, *Uppsala University Uppsala, Sweden*
Mats Olof Karlsson, PhD, *Uppsala University Uppsala, Sweden*
Ron Keizer, PhD, *InsightRX San Francisco, CA, USA*
Terrence Kenakin, PhD, *University of North Carolina, Chapel Hill, Chapel Hill, NC, USA*
Steven E. Kern, Ph.D., *Bill & Melinda Gates Foundation Seattle, WA, USA*
Andrzej Kierzek, PhD, *Certara QSP; Sheffield, United Kingdom*
Hiroaki Kitano, PhD, *The Systems Biology Institute Tokyo, Japan*
Charlotte Kloft, PhD, *Freie Universitaet Berlin Berlin, Germany*
Joerg Lippert, PhD, *Bayer Healthcare Pharmaceuticals Leverkusen, Germany*
Phil Lowe, PhD, *Novartis Pharma AG Basel, Switzerland*
Wei Lu, PhD, *Peking University/Pfizer Pharmacometrics Beijing, China*
Efthymios Manolis, MSc, *European Medicines Agency London, United Kingdom*
Peter Milligan, PhD, *Pfizer Global Research and Development London, United Kindgdom*
Diane R Mould, PhD, FCP, *Projections Research Inc. Phoenixville, PA, USA*
Cynthia J. Musante, PhD, *Pfizer Worldwide Research & Development, Cambridge, MA, USA*
Jerry Nedelman, PhD, *Novartis Pharmaceuticals Corporation East Hanover, NJ, USA*
Kyungsoo Park, MD, PhD, *Yonsei University College of Medicine Seoul, Republic of Korea*
Marc Pfister, MD, FCP, *University of Basel Basel, Switzerland*
Jose Pinheiro, PhD, *Johnson and Johnson Pharmaceutical Research Raritan, NJ, USA*
Saroja Ramanujan, PhD, *Genentech; South San Francisco, CA, USA*
Benjamin Ribba, PhD, *F. Hoffman-La Roche, Basel, Switzerland*
Amin Rostami-Hodjegan, PharmD, PhD, *University of Manchester Manchester, UK*
Malcolm Rowland, DSc, PhD, *University of Manchester Manchester, United Kingdom University of California, San Francisco San Francisco, CA, USA*
Julio Saez-Rodriguez, PhD, *RWTH Aachen University, Aachen, Germany*
Radojka Savic, PhD, *University of California Oakland CA, USA*
Stephan Schmidt, PhD, *University of Florida Orlando, FL, USA*
Virginia D. Schmith, PhD, FCP, *GlaxoSmithKline Zebulon, NC, USA*
Brian Smith, PhD, *Novartis Institutes of Biomedical Research, Inc. Cambridge, MA, USA*
Peter Sorger, PhD, *Harvard Medical School Cambridge, MA, USA*
Joe Standing, PhD, *University College London London, United Kingdom*
Yuichi Sugiyama, PhD, *Riken Innovation Center Sugiyama Laboratory Yokohama, Japan*
Hiroshi Suzuki, PhD, *The University of Tokyo Hospital Tokyo, Japan*
Joel Tarning, PhD, *Mahidol-Oxford Tropical Medicine Research Unit Bangkok, Thailand*
Nicholas Tatonetti, PhD, *Columbia University New York, NY, USA*
Iñaki F. Trocóniz, PharmD, PhD, *University of Navarra Pamplona, Spain*
Natal van Riel, PhD, *Eindhoven University of Technology, Eindhoven, the Netherlands*
An Vermeulen, PhD, *Janssen Research and Development Beerse, Belgium*
Alexander A. Vinks, PharmD, PhD, FCP, *University of Cincinnati, College of Medicine Cincinnati, OH, USA*
Hua Xu, PhD, *University of Texas Health Science Center Houston, Texas, USA*
Ping Zhang, PhD, *IBM T. J. Watson Research Center Yorktown Heights, NY, USA*

Overview

CPT: Pharmacometrics & Systems Pharmacology (CPT:PSP) is an official open access journal of the American Society for Clinical Pharmacology and Therapeutics (ASCPT) and International Society of Pharmacometrics (ISoP).

CPT: Pharmacometrics & Systems Pharmacology is a cross-disciplinary journal devoted to publishing advances in quantitative (e.g., modeling and simulation) methods as applied in pharmacology, physiology and therapeutics in humans. The journal welcomes original research articles, reviews and tutorials that bridge the following areas: pharmacometrics, modeling and simulation as applied to the design and evaluation of clinical trials, systems pharmacology modeling, particularly with a mechanistic link to human (patho)physiology, disease modeling, "population" or mixed-effects pharmacokinetics and pharmacodynamics (PKPD) modeling, modeling and simulation to support translational research, physiologically-based pharmacokinetics (PBPK), model-based meta-analyses of clinical trials, mechanism-based pharmacokinetic-pharmacodynamic modeling, computational pharmacology, bioinformatics, comparative efficacy, effectiveness and cost-effectiveness. Systems pharmacology may involve the application of systems biology approaches to study drug activities, targets and effects. The discipline is often defined with reference to engineering and pharmacological principles as the quantitative analysis of the dynamic interactions between drugs and a biologic system that aims to understand the behavior of the system as a whole. The common focus will be on quantitative methods that improve our understanding of pharmacology and therapeutics in humans.

Abstracting and Indexing
- Embase (Elsevier)
- SCOPUS (Elsevier)
- MEDLINE/PubMed indexing

Society Information
The American Society for Clinical Pharmacology and Therapeutics (ASCPT) was founded in 1900, and consists of over 2,200 professionals whose primary interest is to advance the science and practice of clinical pharmacology and translational medicine for the therapeutic benefit of patients and society. ASCPT is the largest scientific and professional organization serving the disciplines of Clinical Pharmacology and Translational Medicine.

All articles published in this journal are freely available to read, download, and share. Articles are published under the terms of the Creative Commons Attribution Non-Commercial License which permits use, distribution, and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Disclaimer
The Publisher, the American Society for Clinical Pharmacology and Therapeutics, the International Society of Pharmacometrics, and Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the Publisher, the American Society for Clinical Pharmacology and Therapeutics, the International Society of Pharmacometrics, and Editors, neither does the publication of advertisements constitute any endorsement by the Publisher, the American Society for Clinical Pharmacology and Therapeutics, the International Society of Pharmacometrics, and Editors of the products advertised.

Publisher
CPT: Pharmacometrics & Systems Pharmacology is published by Wiley Periodicals, Inc., 350 Main Street, Malden, MA 02148; Telephone: 781-388-8200; Fax: 781-388-8210.

CPT: Pharmacometrics & Systems Pharmacology

CONTENTS

EDITORIAL

151 Precision Medicine in Pharmacometrics and Systems Pharmacology
L Li

PERSPECTIVE

153 Implementing Genomic Clinical Decision Support for Drug-Based Precision Medicine
RR Freimuth, CM Formea, JM Hoffman, E Matey, JF Peterson and RD Boyce

TUTORIAL

156 Building Confidence in Quantitative Systems Pharmacology Models: An Engineer's Guide to Exploring the Rationale in Model Design and Development
J Timmis, K Alden, P Andrews, E Clark, A Nellis, B Naylor, M Coles and P Kaye

ORIGINAL ARTICLES

168 IODNE: An Integrated Optimization Method for Identifying the Deregulated Subnetwork for Precision Medicine in Cancer
S Mounika Inavolu, J Renbarger, M Radovich, V Vasudevaraja, GH Kinnebrew, S Zhang and L Cheng

177 Systems Pharmacology-Based Discovery of Natural Products for Precision Oncology Through Targeting Cancer Mutated Genes
J Fang, C Cai, Q Wang, P Lin, Z Zhao and F Cheng

188 CATTLE (CAncer Treatment Treasury with Linked Evidence): An Integrated Knowledge Base for Personalized Oncology Research and Practice
E Soysal, H-J Lee, Y Zhang, L-C Huang, X Chen, Q Wei, W Zheng, JT Chang, T Cohen, J Sun and H Xu

197 Prediction of *In Vivo* and *In Vitro* Infection Model Results Using a Semimechanistic Model of Avibactam and Aztreonam Combination Against Multidrug Resistant Organisms
SKB Sy, L Zhuang, H Xia, M-E Beaudoin, VJ Schuck and H Derendorf

208 Mathematical Modeling of the Effects of CK2.3 on Mineralization in Osteoporotic Bone
A Lisberg, R Ellis, K Nicholson, P Moku, A Swarup, P Dhurjati and A Nohe

216 Reviewer Acknowledgement